REMARKS/ARGUMENTS

The Claim Amendments

The claims are amended herewith to call for "improving the bioavailability" of the inventive cyclodextrin/carotenoid complexes, commensurate with the disclosure and data presented in the application. The Examiner noted in the outstanding Office action that the data, disclosure, and arguments would be more favorably viewed if the invention were drawn to improving the bioavailability of cyclodextrin/carotenoid complexes. The claims now so read. No new matter is added by virtue of these amendments and their entry respectfully requested.

The Claim Rejections

A. Claims 1-10

Claims 1-10 stand finally rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Leuenberger (U.S. Patent No. 5,221,735), Fukamachi (U.S. Patent No. 4,929,774), Patel (U.S. Patent No. 6,569,463), Orthoefer (U.S. Patent No. 4,125,630), and copending application serial number 10/309,999 (hereinafter, "USSN '999").

Additionally, claim 9 now stands rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Patel in view of USSN '999.

B. Claims 11-20

Claims 11-20 stand finally rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Leuenberger, Fukamachi, Patel, Orthoefer, and USSN '999.

Additionally, claims 4,8,14, and 18 now stand rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Patel in view of USSN '999.

Additionally, claim 19 now stands rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Patel in view of USSN '999.

C. Claims 1-3, 5-7, 9-13, 15-17, and 19-20

Claims 1-3, 5-7, 9-13, 15-17, and 19-20 continue to stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of co-pending USSN '999.

D. Claims 1-3, 5-7, 9-13, 15-17, and 19-20

Claims 1-3, 5-7, 9-13, 15-17, and 19-20 now stand finally rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over USSN '999.

1. The Previously Cited Art

Leuenberger, Fukamachi, Patael, and Orthoefer were reviewed in detail in Applicant's response of December 21, 2004.

2. Copending Application USSN '999

While it still is Applicants' position that this is not available as a reference, the present invention clearly is patentable over the disclosure of this application. That is, this application only enables spray drying and equates all forms of drying, including freeze-drying. Thus, there is no way that the inventors of this application could have known that freeze-drying would be so superior to the forms of drying. Data testifying to this fact has been presented and not rebutted.

While Applicants believe that the foregoing results alone deserve patent protection, there in one more element in independent claims 1 and 11 that also needs to be discussed—the excipient of choice: "a vegetable oil". USSN '999 discloses coatings, which may be "an oil, a natural polymer or a synthetic polymer." (¶ 012 in USSN '999). The data in Example 5 in the present application states that, "freeze-dried lutein/γ-cyclodextrin complex was formulated with medium chain triglycerides (MCT), polysorbate 80, and a combination of lecithin-soybean oil. The formulations were dispersed in PBS and treated with lipase to simulate the digestive process before incorporation into the culture medium." The results reported in Table 5 show both 6-hour and a 24-hour incubation cellular lutein uptake percent increases that are from about 8 to 15 times more uptake at 6 hours and from almost 4 to about 34 times more uptake at 24 hours. Again, while vegetable oil excipients are known in the art, the unexpected bioavailability of freeze-dried carotenoid/cyclodextrin complex with vegetable oil excipients, as set forth in the claims under examination, is not known in the art. Importantly, also, there is no disclosure in the art that would lead the skilled artisan to predict that freeze-drying in combination with a vegetable oil would result in improved bioavailability. The claims now reflect that the invention is directed to improving the bioavailability of a caretanoid.

Thus, the present claims, then, are patentable over USSN '999.

3. Combination of Leuenberger, Fukamachi, Patel, Orthoefer, and USSN '999

With respect to the inclusion of a vegetable oil and the freeze-drying of the complex, Leuenberger describes use of oil to dissolve/disperse carotenoids followed by emulsification with water. Fukamachi describes use of vegetable oils in microencapsulation formulations for oxidation sensitive compounds and mentions lutein and zeaxanthin. However, the oils are used

for making an emulsion with the gelatin matrix, an application entirely different from using the oil as an excipient or filler for the cyclodextrin complex, as in the present invention. Orthoefer teaches using triglycerides as plasticizers for making meat analogs from vegetable proteins, again an application entirely different from formulating a carotenoid-cyclodextrin complex into a dosage form as in the present invention. Patel teaches the use of surfactants in the formulation. Again, it is not obvious from these teachings whether a carotenoid cyclodextrin complex can be formulated with these excipients without any adverse effects on the stability of the complex or the bioavailability.

Dr. Madhavi's first declaration spoke to this issue also. She noted that the weak cyclodextrin/carotenoid bonds could be disrupted by a number of factors, including, *inter alia*, excipients used in formulations, including, *inter alia*, vegetable oils, medium chain triglycerides, and synthetic surfactants such as polysorbates, polyethylene glycols, and phospholipids such as lecithin. She continued that excipients with different polarities could interact with cyclodextrins resulting in the dissociation of the complex, inhibit the release of the actives, or modulate the dissolution properties. The interactions in general are often unpredictable in her expert opinion. Dr. Madhavi cites several publications on the interactions of cyclodextrin inclusion complexes of pharmaceuticals and flavor compounds with formulation excipients.

Again, the art combination structured in the claims rejections do not provide the certainty in teaching regarding the vegetable oil portion of the inventive product and process insofar as expected stability of the complex is concerned, nor the freeze-drying recovery of the carotenoid complex, nor importantly the combination of freeze-drying and use of vegetable oil. The art, then, falls far short of rendering unpatentable the present invention.

With respect to the drying method used in forming the complex, Dr. Madhavi emphasized the data reported in the working examples in the above-identified application. She stated that the invention describes a commercially efficient process, which includes freeze-drying an aqueous dispersion of carotenoid-cyclodextrin complex. Freeze-drying was found to be efficient as compared to spray-drying with a 95% recovery of the product, as compared to 50% loss with spray-drying. Further, to her surprise, the freeze-dried product was superior to spray dried product in bioavailability studies. This unexpectedness is not dispelled or compromised just because freeze-drying is known in the art. The '099 application merely recites a laundry list of dewatering methods without favoring any of them. The data in the '099 application, however, teaches a favored recovery method by reducing spray-drying to practice. The unexpectedness is that for Applicants' product only freeze-drying provided improved

bioavailability for the product along with improved yields of product. Such unexpectedness testifies to the invention, which cannot be predicted from the cited art combination.

Dealing with the soft gel issue (claim 11), Dr. Madhavi noted that it is well known in the art that hydrophobic compounds present delivery challenges because of their physicochemical properties and soft gelatin capsules may offer a delivery system. However, complexation of carotenoids with cyclodextrins in general resulted in a hydrophilic, water dispersible fine powder. Such complexes have been used for making directly compressible tablets or incorporated in to hard gelatin capsules, as cyclodextrins are expected to stabilize sensitive compounds against degradation. However, Dr. Madhavi and her co-inventor found that complexation with cyclodextrins did not stabilize the carotenoids to afford the necessary commercially accepted shelf life in tablets or hard capsules. The soft-gelatin formulation was developed to stabilize the carotenoids. Again, this cannot be predicted and is unexpected, especially when combined with freeze-drying and use of a vegetable oil to disperse the carotenoid complex.

Dr. Madhavi further stated in her first declaration that when hydrophobic excipients, such as vegetable oils, are used, they may inhibit the dispersion of the complex in water; thus, reducing the uptake of the active molecule. However, to her surprise, she found that the complex retained its properties even after formulation with vegetable oil or vegetable oil-lecithin as excipients.

Dr. Madhavi concluded that, in her opinion, it was totally unexpected that a commercially feasible, practical, and commercially viable process resulted for making a bioavailable cyclodextrin/carotenoid complex by freeze-drying a cyclodextrin/carotenoid complex in a molar ratio of between about 0.5:1 and 10:1, and adding such freeze-dried complex to a vegetable oil. Converting such complex to a soft gelatin capsule (claim 11) even further defines the invention over the cited art combination. The art cited simply does not render obvious the present invention in her expert opinion.

4. Summary

In view of the remarks, previously submitted declarations, claim amendments, and the remarks herewith, allowance of all claims and passage to issue of this application respectfully is requested. If allowance is not forthcoming, please enter this amendment for purposes of appeal.

Respectfully submitted,

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